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(19)

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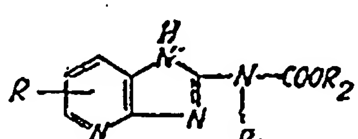
IMIDAZO[4,5-b]PYRIDINE DERIVS — ANTHELMINTICS OF LOW TOXICITY

(54) IMIDAZO[4,5-b]PYRIDINE DERIVATIVES

(71) We, RHONE-POULENC S.A., a French Body Corporate of 22, Avenue Montaigne, Paris 8e, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

THIS INVENTION relates to new therapeutically useful imidazo[4,5 - b]pyridine derivatives and acid addition and quaternary ammonium salts thereof, to processes for their preparation and pharmaceutical compositions containing them.

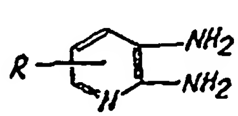
The new imidazo[4,5 - b]pyridine derivatives of the present invention are those of the general formula:



I

wherein R represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, R_1 represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, and R_2 represents an alkyl radical containing 1 to 4 carbon atoms, and acid addition and quaternary ammonium salts thereof.

According to a feature of the invention, the compounds of general formula I wherein R_1 represents a hydrogen atom are prepared by the process which comprises reacting a diaminopyridine of the general formula:



II

(wherein R is as hereinbefore defined) with an isothiourea of the general formula:—

$$R_2OCO—N=C(SCH_3)—NH—COOR_2 \quad \text{III}$$

wherein R_2 is as hereinbefore defined. The reaction is generally carried out in an aqueous acid medium, e.g. aqueous acetic acid, at a temperature between 50° and 100°C.

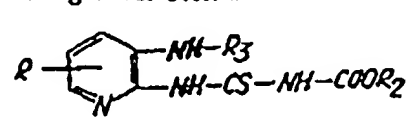
The diaminopyridines of general formula II can be prepared according to the method of Lapin and Slezak, J. Amer. Chem. Soc., 72, 2806 (1950), by reduction of the corresponding 2 - amino - 3 - nitropyridines which themselves can be prepared by the method of Pino and Zehrung, J. Amer. Chem. Soc., 77, 3154 (1955). The diaminopyridines of general formula II can also be prepared by the method of Graboyes and Day, J. Amer. Chem. Soc., 79, 6421 (1957).

The isothioureas of general formula III can be obtained by reaction of an alkyl halogenoformate of the general formula:

$$Hal—COOR_2 \quad \text{IV}$$

(wherein Hal represents a halogen atom and R_2 is as hereinbefore defined) with 2 - methylisothiourea.

According to a further feature of the invention, the compounds of general formula I wherein R_1 represents a hydrogen atom are prepared by the process which comprises the cyclisation by heating of a pyridine derivative of the general formula:



V

[Price 25p]

wherein R_3 represents a hydrogen atom or a grouping —CS—NH—$COOR_2$, and R and R_2 are as hereinbefore defined. The reaction is generally carried out in an acid medium, such as acetic acid in water, and in the presence of a copper salt, e.g. cuprous acetate, and advantageously at the reflux temperature of the reaction mixture.

The pyridine derivatives of general formula V can be obtained by reaction of an isothiocyanate of the general formula:

$$S=C=N—COOR_2 \qquad VI$$

(wherein R_2 is as hereinbefore defined) with a diaminopyridine of general formula II. The reaction can generally be carried out in an inert organic solvent at a temperature of about 25°C.

According to another feature of the invention, the compounds of general formula I wherein R_1 represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms are prepared by the process which comprises reacting a cyanamide of the general formula:

$$R_1—NH—CN \qquad VII$$

(wherein R_1 is as hereinbefore defined) with an alkyl halogenoformate of general formula IV, and reacting the resulting compound of the general formula:

$$R_1—N(COOR_2)—CN \qquad VIII$$

(wherein R_1 and R_2 are as hereinbefore defined) with a diaminopyridine of general formula II. The reactions can generally be carried out in an inert organic solvent and at a temperature between 0° and 50°C.

The imidazo[4,5 - *b*]pyridine derivatives of general formula I obtained by the aforementioned processes can be purified by physical methods such as distillation, crystallisation or chromatography, or by chemical methods such as the formation of salts, crystallisation of the salts and decomposition of them in an alkaline medium. In carrying out the said chemical methods the nature of the anion of the salt is immaterial, the only requirement being that the salt be well-defined and readily crystallisable.

The imidazo[4,5 - *b*]pyridine derivatives of the general formula I may be converted by methods known *per se* int acid addition and quaternary ammonium salts. The acid addition salts may be obtained by the action of acids on the imidazo[4,5 - *b*]pyridine derivatives in appropriate solvents. As organic solvents there may be used alcohols, ketones, ethers or chlorinated hydrocarbons. The salt which is formed is precipitated, if necessary after concentration of the solution, and is isolated by filtration or decantation. The quaternary ammonium salts may be obtained by the action of esters on the imidazo[4,5 - *b*]pyridine bases, optionally in an organic solvent, at room temperature or, more rapidly, with gentle heating.

The imidazo[4,5 - *b*]pyridine derivatives of the present invention, and their acid addition and quaternary ammonium salts, possess useful anthelmintic properties associated with a low toxicity. (The imidazo[4,5 - *b*]pyridine derivatives conforming to general formula I obtained as products in the following Examples are all atoxic to mice at 1 g./kg. animal body weight when administered orally). They have shown themselves particularly active against experimental infestations in mice of *Nippostrongylus muris* and *Nematospiroides dubius* at doses of between 200 and 1,000 mg./kg. animal body weight when administered orally, in dogs of *Ankylostoma caninum, Uncinaria stenocephala, Toxocara canis, Toxascaris leonina, Trichuris vulpis, Taenia sp.* and *Dipylidium caninum* at doses of between 15 and 150 mg./kg. animal body weight when administered orally, and in sheep of *Haemonchus contortus, Trichostrongylus axei, Ostertagia circumcincta, Trichostrongylus colubriformis, Nematodirus battus and Dictyocaulus filaria* at doses of between 15 and 100 mg./kg. animal body weight when administered orally. Generally, two administrations of the compounds, the second six hours after the first, are effective in counteracting the helminth infestations. *In vitro*, the compounds have shown activity against larvae of digestive threadworms of horses.

Preferred compounds of the invention are those wherein R_1 in general formula I represents a hydrogen atom, and more especially those compounds wherein R and R_1 represent hydrogen atoms and R_2 represents a methyl or ethyl radical, i.e. 2 - methoxycarbonylamino - imidazo[4,5 - *b*]pyridine and 2 - ethoxycarbonylamino - imidazo[4,5 - *b*]pyridine, and acid addition and quaternary ammonium salts thereof.

For therapeutic purposes, the imidazo[4,5 - *b*]pyridine derivatives of general formula I may be employed as such or in the form of non-toxic acid addition salts, i.e. salts containing anions which are relatively innocuous to the animal organism in therapeutic doses of the salts (such as hydrochlorides, sulphates, nitrates, phosphates, acetates, propionates, succinates, benzoates, fumarates, maleates, tartrates, theophylline-acetates, salicylates, phenolphthalinates and methylene - bis - β - hydroxynaphthoates) so that the beneficial physiological properties inherent in the bases are not vitiated by side-effects ascribable to the anions. However,

they may also be employed in the form of non-toxic quaternary ammonium salts obtained by reaction with organic halides, e.g. methyl, ethyl, allyl or benzyl chloride, bromide or iodide, or other reactive esters, e.g. methyl- or ethyl - sulphates, benzene - sulphonates or toluene - *p* - sulphonates.

The following Examples illustrate the invention.

EXAMPLE 1

2,3 - Diaminopyridine (21.8 g.) is added to a suspension of 1,3 - diethoxycarbonyl - 2 - methylisothiourea (46.8 g.) in water (200 cc.) and acetic acid (36 g.), and the mixture is heated at 80—90°C. until the evolution of gas ceases. After cooling, the precipitate which appears is filtered off, washed with acetone (3×50 cc.) and taken up in N hydrochloric acid (200 cc.). The hydrochloric acid solution obtained after filtration is neutralised by the addition of solid potassium bicarbonate (20 g.). The precipitate which appears is filtered off and dried under reduced pressure (0.5 mm. Hg.) at 20°C. to yield 2 - ethoxycarbonylamino - imidazo-[4,5 - *b*]pyridine (22.7 g.) melting at 285°C. with decomposition.

2,3 - Diaminopyridine, melting at 115—116°C., employed as starting material can be prepared from 2 - aminopyridine according to the method described in Org. Synth. *44*, 34 (1964).

The 1,3 - Diethoxycarbonyl - 2 - methylisothiourea, melting at 46°C., can be obtained by the action of ethyl chloroformate on 2 - methylisothiourea.

EXAMPLE 2

A mixture of 1,3 - dimethoxycarbonyl - 2 - methylisothiourea (22.3 g.), 2,3 - diaminopyridine (11.8 g.) in water (108 cc.) and acetic acid (19.4 g.) is heated at 90—95°C. until the evolution of gas ceases. The reaction mixture is then treated as described in Example 1 to yield 2 - methoxycarbonylamino - imidazo[4,5 - *b*]pyridine (10.9 g.) melting at 305—307°C. with decomposition.

1,3 - Dimethoxycarbonyl - 2 - methylisothiourea, melting at 100°C., employed as starting material can be obtained by the action of methyl chloroformate on 2 - methylisothiourea.

EXAMPLE 3

1,3 - Dimethoxycarbonyl - 2 - methylisothiourea (12.5 g.) is added, with agitation, to a suspension of 2,3 - diamin - 6 - methylpyridine (7.43 g.) in distilled water (60 cc.) and acetic acid (10.9 g.), and the mixture is heated at 81°C. for 5 hours. After cooling, the suspension obtained is filtered and the resulting solid is washed with distilled water (4×10 cc.) and then with acetone (2×10 cc.). The product obtained (7.6 g.) is dissolved in N hydrochloric acid (41 cc.). After treatment with decolourising charcoal, the solution obtained is filtered and to the filtrate is added a solution of sodium bicarbonate (3.5 g.) in water (35 cc.). The solid which appears is filtered off, washed with distilled water (5×10 cc.) and then with acetone (2×20 cc.) to yield 2 - methoxycarbonylamino - 5 - methyl - imidazo[4,5 - *b*]pyridine (7 g.) melting at 271—272°C.

EXAMPLE 4

1,3 - Dimethoxycarbonyl - 2 - methylisothiourea (26.5 g.) is added, with agitation, to a suspension of 2,3 - diamino - 5 - methylpyridine (15.7 g.) in distilled water (128 cc.) and acetic acid (23 g.), and the mixture is heated at 90°C. for 3 hours. After cooling, the suspension obtained is filtered, the resulting solid washed with distilled water (4×30 cc.) and then with acetone (2×30 cc.). The product obtained (11.7 g.) is dissolved in acetic acid (60 cc.) under reflux. After treatment with decolourising charcoal, the resulting solution is filtered and, on cooling the filtrate, a solid appears and is filtered off, washed with acetic acid (2×5 cc.) and then with anaesthetic grade diethyl ether (3×20 cc.) to yield 2 - methoxycarbonylamino - 6 - methyl - imidazo[4,5 - *b*]-pyridine (9.3 g.) decomposing at 365—368° C. before melting.

EXAMPLE 5

A suspension of 2 - (3 - methoxycarbonyl - thioureido) - 3 - aminopyridine (5.26 g.), and cuprous acetate (2 g.) in water (20 cc.) and acetic acid (20 cc.) is heated at 102°C. for 5 hours. The suspension obtained is then filtered and the filtrate made alkaline by the addition of ammonium hydroxide solution (d=0.92) until the pH is 8. A solid appears which is filtered off, washed with distilled water (3×5 cc.) to yield 2 - methoxycarbonylamino - imidazo[4,5 - *b*]pyridine (0,6 g.) melting at 285—290°C.

2 - (3 - Methoxycarbonyl - thioureido) - 3 - aminopyridine (15.5 g.), which decomposes at 230°C., employed as starting material can be prepared by reacting methyl isothiocyanatoformate (15.2 g.) with 2,3 - diaminopyridine (28.4 g.) in acetonitrile (370 cc.) at 25°C.

The present invention also includes pharmaceutical and veterinary compositions which comprise, as the active ingredient, at least one imidazo[4,5 - *b*]pyridine derivative of general formula I, or a non-toxic acid addition or quaternary ammonium salt thereof, in association with a carrier or coating generally used in the preparation of pharmaceutical and veterinary compositions. The compositions are preferably in a form suitable for oral administration.

Tablets, pills, powders or granules can be used as solid compositions for oral administration. In these compositions the imidazo[4,5 - *b*]pyridine compound is mixed with one or more inert diluents, such as sucrose, lactose or starch. These compositions can also contain substances other than diluents, for example lubricants such as magnesium stearate.

Pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs, containing inert diluents such as water or paraffin oil, can be used as liquid compositions for oral administration. These compositions can also contain substances other than the diluents, such as for example, wetting agents, or sweetening, flavouring or aromatizing agents.

In veterinary therapy, the imidazo[4,5 - *b*]pyridine derivatives can be used for the treatment of cestodal or nematodal helminthiases of cattle, sheep, goats, dogs and domestic animals in general, at single dosages of between 15 and 150 mg./kg. animal body weight, administered orally.

In human therapy, the imidazo[4,5 - *b*]-pyridine derivatives can be used to eliminate oxyworms and cestodes at single dosages of between 10 and 50 mg./kg. administered orally. These dosages can be repeated at regular intervals of several days or several weeks to achieve definitive removal of the parasite.

In general, the physician or veterinary surgeon will decide the posology which is considered most appropriate, depending on the species in question as well as the age, the weight, the degree of infection and all other factors peculiar to the subject to be treated.

The following Example illustrates therapeutic compositions according to the invention.

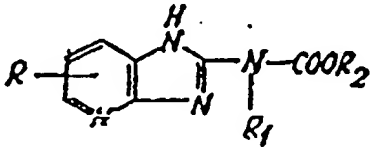
EXAMPLE 6

Tablets, weighing 0.7 g., having the following composition are prepared in accordance with the usual technique:

2 - methoxycarbonylamino - imidazo[4,5 - *b*]pyridine	0.500 g.
wheat starch	0.150 g.
colloidal silica	0.040 g.
magnesium stearate	0.010 g.

WHAT WE CLAIM IS:—

1. Imidazo[4,5 - *b*]pyridine derivatives of the general formula:



wherein R represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, R_1 represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, and R_2 represents an alkyl radical containing 1 to 4 carbon atoms, and acid addition and quaternary ammonium salts thereof.

2. Imidazo[4,5 - *b*]pyridine compounds according to claim 1 wherein R_1 represents a hydrogen atom and R and R_2 are as defined in claim 1.

3. Imidazo[4,5 - *b*]pyridine compounds according to claim 1 wherein R and R_1 represent hydrogen atoms and R_2 is as defined in claim 1.

4. 2 - Methoxycarbonylamino - imidazo-[4,5 - *b*]pyridine and acid addition and quaternary ammonium salts thereof.

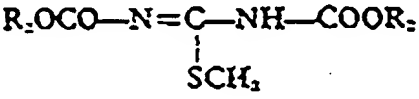
5. 2 - Ethoxycarbonylamino - imidazo-[4,5 - *b*]pyridine and acid addition and quaternary ammonium salts thereof.

6. 2 - Methoxycarbonylamino - 5 - methyl - imidazo[4,5 - *b*]pyridine and acid addition and quaternary ammonium salts thereof.

7. 2 - Methoxycarbonylamino - 6 - methyl - imidazo[4,5 - *b*]pyridine and acid addition and quaternary ammonium salts thereof.

8. Process for the preparation of imidazo-[4,5 - *b*]pyridine derivatives of the general formula specified in claim 1 wherein R_1 represents a hydrogen atom which comprises reacting a diaminopyridine of the general formula:

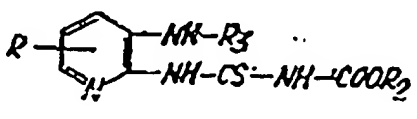
(wherein R is as defined in claim 1) with an isothiourea of the general formula:



wherein R_2 is as defined in claim 1.

9. Process according to claim 8 in which the reaction is carried out in an aqueous acid medium at a temperature between 50° and 100°C.

10. Process for the preparation of imidazo-[4,5 - *b*]pyridine derivatives of the general formula specified in claim 1 wherein R_1 represents a hydrogen atom which comprises cyclising by heating a pyridine derivative of the general formula:



wherein R_3 represents a hydrogen atom or a grouping —CS—NH—$COOR_2$, and R and R_2 are as defined in claim 1.

11. Process according to claim 10 in which cyclisation of the pyridine derivative is carried out in an acid medium and in the presence of a copper salt.

12. Process according to claim 10 or 11 in which cyclisation of the pyridine derivative is carried out in aqueous acetic acid in the presence of cuprous acetate.

13. Process for the preparation of imidazo[4,5 - *b*]pyridine derivatives as claimed in claim 1 which comprises reacting a cyanamide of the general formula:

$$R_1—NH—CN$$

(wherein R_1 is as defined in claim 1) with an alkyl halogeneformate of the general formula:

$$Hal—COOR_2$$

(wherein Hal represents a halogen atom and R_2 is as defined in claim 1), and the resulting compound of the general formula:

$$R_1—N(COOR_2)—CN$$

is reacted with a diaminopyridine of the general formula specified in claim 8.

14. Process according to claim 13 wherein the reactions are carried out in an inert organic solvent and at a temperature between 0° and 50°C.

15. Process according to claim 8, 9, 13 or 14 followed by the step of converting by methods known *per se* an imidazo[4,5 - *b*]-pyridine base thus obtained into an acid addition or quaternary ammonium salt.

16. Process according to claim 10, 11 or 12 followed by the step of converting by methods known per se an imidazo[4,5 - *b*]-pyridine base thus obtained into an acid addition or quaternary ammonium salt.

17. Process for the preparation of imidazo[4,5 - *b*]pyridine derivatives of the general formula specified in claim 1 substantially as described in Example 1 or 2.

18. Process for the preparation of imidazo-[4,5 - *b*]pyridine derivatives of the general formula specified in claim 1 substantially as described in Example 3 or 5.

19. Process for the preparation of imidazo-[4,5 - *b*]pyridine derivatives of the general formula specified in claim 1 substantially as described in Example 4.

20. Imidazo[4,5 - *b*]pyridine derivatives of the general formula specified in claim 1 and acid addition and quaternary ammonium salts thereof when prepared by the process claimed in claim 8, 9, 13, 14, 15 or 17.

21. Imidazo[4,5 - *b*]pyridine derivatives of the general formula specified in claim 1 and acid addition and quaternary ammonium salts thereof when prepared by the process claimed in claim 10, 11, 12, 16, 18 or 19.

22. Pharmaceutical and veterinary compositions which comprise, as active ingredient, at least one imidazo[4,5 - *b*]pyridine derivative as claimed in any one of claims 1 to 5, or a non-toxic acid addition or quaternary ammonium salt thereof, in association with a carrier or coating used in the preparation of pharmaceutical and veterinary compositions.

23. Pharmaceutical and veterinary compositions according to claim 22 which comprise, as active ingredient, the imidazo[4,5 - *b*]pyridine derivative claimed in claim 6, or a non-toxic acid addition or quaternary ammonium salt thereof.

24. Pharmaceutical and veterinary compositions according to claim 22 which comprise, as active ingredient, the imidazo[4,5 - *b*]pyridine derivative claimed in claim 7, or a non-toxic acid addition or quaternary ammonium salt thereof.

25. Pharmaceutical compositions according to claim 22 substantially as hereinbefore described with especial reference to Example 6.

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